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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
KAUFMAN, CLAIRE M

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/042,583	Applicant(s) NI, ET AL.	
	Examiner Claire M. Kaufman	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2001 and 24 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *287-622* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *see continuation* is/are allowed.

6)☒ Claim(s) *see continuation* is/are rejected.

7)☒ Claim(s) *see continuation* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continuation of Form 326, Paper #27

Disposition of Claims

5) Claims 300-317, 340-350, 374, 375, 377-380, 382-387, 416, 417, 419-429, 459-474 and 595-606 are allowed.

6) claims 287-299, 318, 319, 326-339, 351, 353-373, 376, 381, 388, 389, 391-415, 418, 430, 431, 433, 458, 475, 476, 478-565, 567-594 and 607-622 are rejected.

7) Claims 320-325, 352, 390, 432, 377 and 566 are objected to.

DETAILED ACTION

Response to Arguments

The rejection of claims are moot in view of the cancellation of the claims. Note new rejections appear below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Interpretation

Claims which recites "mature DR5 polypeptide" (362, 276, 391, 404, 418, 433, 494, 522, 540, and 610) are interpreted by the Examiner to mean that the "mature DR5 polypeptide" is the one disclosed in the specification as the mature form of ATCC 97920 expression product or SEQ ID NO:2 from amino acids +1 to +360 as defined on page 9, lines 5-17, and paragraph bridging pages 9-10. Similarly, the recitiation of "DR5 polypeptide" in claim 609 is interpreted as meaning the disclosed DR5 sequence in the specification that is the expression product of the cDNA of ATCC 97920 or of SEQ ID NO:2 from amino acids -51 to +360 as defined on page 9, lines 5-17, and paragraph bridging pages 9-10. With the Examiner's interpretation, the metes and bounds of the term are clear. If Applicants disagree with this interpretation, then the claims will be subject to a rejection under 35 USC 112, second paragraph, that will not be a new grounds of rejection as the issue has been raised herein.

Claim Objections

Claims 381, 607 and 615 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 381 refers to cancelled claim 96. Claim 607 is a method reciting "the host cell of claim 604", but claim 604 is drawn to a vector. Claim 615 is a method claim reciting "the polynucleotide of claim 606", but claim 606 is drawn to a host cell.

Claims 320-325, 353, 390, 432, 477 and 566 are objected to as depending on a rejected base claim.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 299, 318, 339, 362, 373, 376, 381, 388, 391, 403, 404, 415, 418, 430, 433, 445, 458, 475, 491, 494, 506, 517, 522, 534, 540, 552, 564, 579, 594, 607-610 and 622 and dependent claims 405-414, 443-445, 504, 523-526, 532-533, 620, 621 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 381 recites the limitation "claim 96". There is insufficient antecedent basis for this limitation in the claim. Claim 96 has been canceled.

Claim 607 recites the limitation "host cell of claim 604" in line 2. There is insufficient antecedent basis for this limitation in the claim. Claim 604 is drawn to a vector.

Claim 615 recites the limitation "polynucleotide of claim 606". There is insufficient antecedent basis for this limitation in the claim.

Claims 299, 318, 339, 373, 388, 403, 415, 430, 445, 458, 475, 491, 506, 517, 534, 552, 564, 579, 594, 607 and 622 are indefinite because it is not clear to which polypeptide "said polypeptide" in the second line is referring. The claims are "A method of producing **a** polypeptide comprising culturing the host cell of claim xxx under conditions such that said polypeptide is expressed,..." Claim xxx generally recites "An isolated polynucleotide comprising a nucleic aid which encodes a polypeptide comprising...." The problem is, that the preamble of the instantly rejected claim states "a polypeptide" without being more specific, and even though the host cell of claim xxx is cultured, it is not clear that it is said polypeptide of claim xxx being expressed from the host cell as opposed to another polypeptide within the host cell. This rejection could be obviated by clarifying what polypeptide is expressed. For example, for claim 299, a phrasing such as "A method of producing the polypeptide encoded by the polynucleotide of claim 287, comprising: (a) culturing a host cell comprising said nucleic acid

under conditions such that said polypeptide is expressed; and (b) recovering said polypeptide." would obviate this rejection.

Claims 362, 376, 391, 404, 418, 433, 494, 522, 540 and 610 are indefinite because it is unclear what is meant by " a polypeptide fragment which is capable of functioning as a functional domain within a mature DR5 polypeptide to induce apoptosis." It is unclear what the spatial relationship of the fragment is to the mature DR5 polypeptide. For example, it is unclear if it is intended that the fragment replaces a corresponding section of a mature DR5 polypeptide so that it is embedded within the remaining portion(s) of the DR5 polypeptide or if the fragment is added to the mature DR5 polypeptide. It is further unclear if the fragment, which is a "functional domain" is solely responsible for the apoptotic function or if it must rely on some part of the mature DR5 polypeptide to induce apoptosis.

Similarly, claim 609 is indefinite because it is unclear what is meant by "a polypeptide fragment which is capable of functioning as a functional domain within a DR5 extracellular domain to bind TRAIL." The intent of the meaning of "functioning as a functional domain within..." is unclear for the reasons set forth in the preceding paragraph.

The rejection of claims 362, 276, 391, 404, 418, 433, 494, 522, 540, 609 and 610 could be obviated by using phrasing such as, for claim 362: "An isolated polynucleotide comprising a nucleic acid which encodes a polypeptide fragment at least 90% identical to amino acids 158-360 of SEQ ID NO:2, and wherein a DR5 variant consisting of amino acids 1 to 360 of SEQ ID NO:2, with the exception that amino acids 158-360 of SEQ ID NO:2 are deleted and replaced with said polypeptide fragment, induces apoptosis *in vitro* when over-expressed in human 293 embryonic kidney cells."

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In the interest of compact prosecution, claims which recite "fragment capable as functioning as a functional domain within a mature DR5 polypeptide to induce apoptosis" are being given the possible meaning that the fragment alone is responsible and sufficient for induction of apoptosis when comprised by a mature DR5 polypeptide. Such claims have been rejected under 35 USC 112, second paragraph, because of the several meanings they can carry. If the above meaning is intended, then the claims are rejected here under 35 USC 112, first paragraph as follows:

Claims 404-415, 418, 433, 494, 522, 540, 609 and 610 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) an isolated polynucleotide comprising a nucleic acid which encodes a polypeptide (a) consisting of an amino acid sequence at least 90% identical to amino acids 1-133 of SEQ ID NO:2 (*i.e.*, the ECD of DR5), wherein said polypeptide binds TRAIL or (b) consisting of an amino acid sequence at least 90% identical to amino acids 158-360 of SEQ ID NO:2 (*i.e.*, the ICD of DR5), wherein said polypeptide induces apoptosis *in vitro* when over-expressed in human 293 embryonic kidney cells, or (2) an isolated polynucleotide comprising a nucleic acid which encodes a polypeptide fragment at least 90% identical to amino acids 273-340 of SEQ ID NO:2, and wherein a DR5 variant consisting of amino acids 1 to 360 of SEQ ID NO:2, with the exception that amino acids 273-340 of SEQ ID NO:2 are deleted and replaced with said polypeptide fragment, induces apoptosis *in vitro* when over-expressed in human 293 embryonic kidney cells, does not reasonably provide enablement for (1) the claimed polynucleotide comprising a nucleic acid which encodes a polypeptide (a) consisting of an amino acid sequence less than 90% identical to amino acids 1-133 of SEQ ID NO:2, which includes sequences smaller than 90% of the length of the full ECD of DR5, wherein said polypeptide must binds TRAIL or (b) consisting of an amino acid sequence less than 90% identical to amino acids 158-360 of SEQ ID NO:2, which includes sequences smaller than 90% of the length of the full ICD of DR5, wherein said polypeptide induces, or (2) an isolated polynucleotide comprising a nucleic acid which encodes a polypeptide fragment at least 90% identical to amino acids 273-340 of SEQ ID NO:2 or a 5-50 contiguous amino acid-long fragment of SEQ ID NO:2 from amino acids 1-360 or 158-360 of SEQ ID NO:2 which induces apoptosis. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make the invention commensurate in scope with these claims

Claim 404 comprises a fragment at least 90% identitcal to amino acids 273-340 of SEQ ID NO:2 and wherein said is fragment capable as functioning as a functional domain within a mature DR5 polypeptide to induce apoptosis". The functional fragment of claim 494 does not need to be longer than 9 contiguous amino acids from residues 1-360 of SEQ ID NO:2. That of claim 522 only needs to be 4-5 amino acids long. That of claim 540 only needs to be 90% identical to 30 contiguous amino acids from 158-360 of SEQ ID NO:2 to induce apoptosis. Claims 609 and 610 require only 50 contiguous amino acids from 1-360 of SEQ ID NO:2 to bind TRAIL or induce apoptosis, respectively.

The specification teaches that the full ECD of the disclosed DR5 is 133 amino acids long. The full ICD, the domain responsible for transducing the apoptotic signal, is 202 amino acids long (see Figs. 1A-B). The specification does not teach fragments of the ECD or ICD that allows the fragment to function out of context. The prior art treaches DR3 and other DR-related polypeptides for which it was known that the full ECD bound a ligand and the full ICD induced apoptosis (*e.g.*,Chinnaiyan et al., Science, 1996, cited by Applicants). The art printed before the effective filing date of the instant application does not teach a DR5. While the death domain has been identified within a DR polypeptide, one would not reasonably expect it to induce apoptosis out of the full, at least, intracellular receptor protein context. What was not known, and for which there is not guidance in the instant specification, was which amino acids within the ECD or ICD are necessary for function and/or which can be substituted or deleted while retaining the required function. Only the basics of the relationship of domain structure to function were known, so the skill in the art is was not high. Since the ECD is 133 amino acids long and because ligand binding is a complex event requiring not only particular amino acids that directly interact with the ligand but also a particular 3-dimensional conformation which those amino acids must be in to be able to interact, the skilled artisan would not have a reasonable expectation that a fragment of 50 amino acids would be sufficient to bind a ligand since binding is a complex stereochemical event. The same general complexity holds for the ICD, which to induce apoptosis must necessarily be able to interact with some intracellular signal transduction system. For these reasons, it would require undue experimentation to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 492-495, 507-508, 518-523, 535-541 and 608-611 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 6,072,047, cited by Applicants.

US Patent No. 6, 072,047 receives priority back to March 12, 1997 (application number 08/815,255) for the DNA fragment encoding the TRAIL-R fragment in Figure 1 of the patent, which is the same as amino acids 336-386 of SEQ ID NO:2 of the patent. This TRAIL receptor fragment is identical to amino acids 256-306 of SEQ ID NO:2, which is encoded by nucleotides 1048-1200 of SEQ ID NO:1, of the instant application. The DNA fragment was obtained after the mature protein had been purified (EXAMPLE 1 and 2) by using degenerate oligonucleotide primers (heterologous polynucleotides) for PCR (EXAMPLE 3). As later shown in US Patent 6,072,047, the above fragment functions within a mature DR5 to induce apoptosis.

Note that because the meaning of functioning as a functional domain is unclear (see rejection under 35 USC 112, second paragraph above), the teachings of '047 appear to meet the reasonable meaning of the terms.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 492-552 and 608-622 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,072,047.

US Patent No. 6, 072,047 receives priority back to March 12, 1997 (application number 08/815,255) for the DNA fragment encoding the TRAIL-R fragment in Figure 1 of the patent, which is the same as amino acids 336-386 of SEQ ID NO:2 of the patent. This TRAIL receptor fragment is identical to amino acids 256-306 of SEQ ID NO:2, which is encoded by nucleotides 1048-1200 of SEQ ID NO:1, of the instant application. The DNA fragment was obtained after the mature protein had been purified by affinity purification with TRAIL (TNF-Related Apoptosis-Inducing Ligand; EXAMPLE 1 and 2) by using degenerate oligonucleotide primers (heterologous polynucleotides) for PCR (EXAMPLE 3). TRAIL receptors binds TRAIL), which had been demonstrated to induce apoptosis in some cancer cells as well as virally infected cells (col. 1, lines 15-22). As later shown in US Patent 6,072,047, the above fragment functions within a mature DR5 to induce apoptosis.

Also taught are methods and means for recombinant cloning and expression vectors containing the TRAIL-R DNA, including: "A method of producing TRAIL-R polypeptides comprising culturing host cells transformed with a recombinant expression vector encoding trail-R, under conditions that promote expression of TRAIL-R, then recovering the expressed TRAIL-R polypeptides from cultures." (col. 8, lines 6-22) The encoding DNA may be operably linked to a suitable regulatory sequence (col. 8, lines 23-40). Also, how to make a polynucleotide encoding fusion protein of TRAIL-R and human Ig Fc region fusion protein in order to make TRAIL-R dimers (col. 13, lines 3—35). Such dimmers are useful for "facile purification by affinity chromatography over Protein A or Protein G columns" (col. 14, lines 9-14 and col. 15,

lines 16-22). US Patent No. 6,072,047 does not teach the actually made products of this paragraph.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a polynucleotide comprising the TRAIL-R DNA fragment opreably linked to a heterologous regulatory sequence as well as a heterologous polynucleotide sequence that encoded a human Ig Fc domain, and a method of making such, as taught by US Patent No. 6,072,047 for well known and suggested purposes of DNA amplification and protein production and purification. Because the DNA fragment of Figure 1 had been identified as encoding part of a TRAIL receptor, one would have been motivated to produce the above described products to characterize aspects of the receptor that binds TRAIL, which was known to be involved in apoptosis and have clinical implications. For these reasons, the invention is *prima facie* obvious.

Claims 287-299, 319, 326-339, 351, 353-373, 389, 391-415, 431, 433-458, 476, 478-491, 553-565 and 567-594 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,072,047.

US Patent No. 6, 072,047 receives priority back to Feb. 13, 1997 (application number 08/799,861) for the isolated mature TRAIL-R protein (SEQ ID NO:2 of patent). US Patent No. 6, 072,047 receives priority back to March 12, 1997 (application number 08/815,255) for the DNA fragment encoding the TRAIL-R fragment in Figure 1 of the patent, which is the same as amino acids 336-386 of SEQ ID NO:2 of the patent. This TRAIL receptor fragment is identical to amino acids 256-306 of SEQ ID NO:2, which is encoded by nucleotides 1048-1200 of SEQ ID NO:1, of the instant application. The DNA fragment was obtained after the mature protein had been purified by affinity purification with TRAIL (TNF-Related Apoptosis-Inducing Ligand; EXAMPLE 1 and 2) by using degenerate oligonucleotide primers (heterologous polynucleotides) for PCR (EXAMPLE 3). TRAIL receptors binds TRAIL, which had been demonstrated to induce apoptosis in some cancer cells as well as virally infected cells (col. 1, lines 15-22). As prophetically stated in priority application 08/799,861 and later shown in US Patent 6,072,047, the above fragment is part of and functions within a mature TRAIL-R to induce apoptosis. The mature TRAIL-R has a sequence identical to amino acids +1 to +360 of SEQ ID NO:2 of the

instant application with the exception that TRAIL-R contains 29 additional amino acids inserted after amino acid residue 131 of SEQ ID NO:2 of the instant application. It is explained in col. 6, lines 6-19, that the TRAIL-R (or fragment thereof) may be encoded by a sequence degenerate to the native sequence of SEQ ID NO:1.

Also taught are methods and means for recombinant cloning and expression vectors containing the TRAIL-R DNA, including: "A method of producing TRAIL-R polypeptides comprising culturing host cells transformed with a recombinant expression vector encoding TRAIL-R, under conditions that promote expression of TRAIL-R, then recovering the expressed TRAIL-R polypeptides from cultures." (col. 8, lines 6-22) The encoding DNA may be operably linked to a suitable regulatory sequence (col. 8, lines 23-40). Also, how to make a polynucleotide encoding fusion protein of TRAIL-R and human Ig Fc region fusion protein in order to make TRAIL-R dimers (col. 13, lines 3—35). Such dimmers are useful for "facile purification by affinity chromatography over Protein A or Protein G columns" (col. 14, lines 9-14 and col. 15, lines 16-22). US Patent No. 6,072,047 does not teach the actually made products of this paragraph.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a polynucleotide comprising a TRAIL-R polynucleotide or fragment opreably linked to a heterologous regulatory sequence as well as a heterologous polynucleotide sequence that encoded a human Ig Fc domain, and a method of making such, as taught by US Patent No. 6,072,047 for well known and suggested purposes of DNA amplification and protein production and purification. Note that the encoding polynucleotide does not have to have the native sequence which encodes TRAIL disclosed in the patent. With the well known knowledge of the degeneracy of the genetic code, one of ordinary skill in the art could have readily envisioned all degenerate sequences that encoded the TRAIL-R protein without knowing what the actual native sequence was. This knowledge was the basis of making the denerate oligo primers of US Patent 6,072,047 that allowed TRAIL-R DNA to be obtained. One would have been motivated to produce the above described products including polynucleotides encoding the mature TRAIL-R as well as fragments to characterize aspects of the receptor that binds TRAIL, which was known to be involved in apoptosis and have clinical implications. It is further noted that "comprising" is open language and when used in a claim before a fragment, allows from more amino acids or

nucleic acids, as the case may be, than recited in the specific fragment. For these reasons, the invention is *prima facie* obvious.

Conclusion

Claims 300-317, 340-350, 374, 375, 377-380, 382-387, 416, 417, 419-429, 459-474 and 595-606 are allowed.

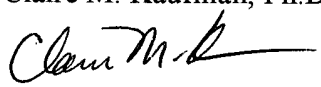
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Thursday from 8:30AM to 12:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (703) 308-6564.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.



Patent Examiner, Art Unit 1646

November 30, 2001